Nano-Man of the Moment
Changing the Way We Think About Medicine
The Howard Hughes Medical Institute has made a gift of $4 million to the U-M Medical School to support a new program in bioinformatics. The interdisciplinary program will include graduate education and research in the emerging field of bioinformatics, which merges recent advances in molecular biology and genetics with advanced computer science technology. The goal is increased understanding of the complex web of interactions linking the individual components of a living cell to the integrated behavior of the entire organism.

“The Human Genome Project and advances in molecular biology have generated a flood of new data about individual components of cells,” says Allen Lichter, M.D., dean of the Medical School. “Yet we know very little about how all these parts work together to create a living organism. The funding from Howard Hughes will help us obtain the computer technology and expertise we need to develop the next generation of bioinformatics tools and educate tomorrow’s scholars in this important new discipline.”

According to Michael A. Savageau, Ph.D., professor and chair of Microbiology and Immunology and director of the bioinformatics program, the Hughes grant will be used to recruit four new junior faculty members and hire technical support staff for a new Bioinformatics Core Facility under construction in the Medical School.

“The Hughes award also will help fund pilot research projects in which bioinformatics faculty and graduate students will work closely with other U-M investigators to develop a deeper understanding of living systems and new applications for this technology,” Savageau says.

“This major grant from the Howard Hughes Institute complements a substantial investment made by the U-M Health System,” says Gil Omenn, M.D., Ph.D., executive vice president for medical affairs. “As part of our Life Sciences Initiative, we want to help shape the future directions of concepts, modeling and analysis in bioinformatics and biocomplexity.” The U-M Health System has committed $5 million to bioinformatics, matched by $5 million from Parke-Davis, a division of Warner-Lambert.

The Medical School is one of 41 medical schools selected this year to receive a Howard Hughes Medical Institute grant for biomedical research support. More than 320 Hughes investigators, including seven in the U-M Medical School, conduct medical research in Howard Hughes Medical Institute laboratories at 71 medical centers and universities nationwide.

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Medical School Ranks Ninth Nationally in 1999 NIH Research Awards

The National Institutes of Health have nearly doubled funding for medical research at the University of Michigan Medical School over the past eleven years, making the school ninth in the nation and third among public universities in total grants from the NIH.

The NIH awarded a record $156.5 million to Medical School investigators in fiscal year 1999, up from $136.2 million in 1998 and $79.7 million in 1989. In both of those previously historical years, the school ranked tenth among NIH-funded institutions.

Last year, the allocations funded 451 individual research awards — the sixth largest total in the nation. Training grants, fellowships, research and development contracts, and other awards are also included in the total.

“As we celebrate our school’s 150th anniversary, we’re excited by the prospect of the new knowledge and therapies that will surely arise from this unprecedented level of funding for our faculty,” says Allen Lichter, M.D., dean of the Medical School.

Lichter attributes the steady rise in NIH funding to the research faculty’s productivity and responsiveness to national medical needs. Not only are the NIH awards a majority of the Medical School’s external funding, but they also make up a large percentage of the University’s total research funds. Medical School NIH awards make up nearly 68 percent of all NIH funding at the University, helping make Michigan sixth in the nation in NIH award totals at higher education institutions.

When all sources of funding — including other federal and state agencies, corporations, and foundations — are totaled, Medical School researchers were awarded $204.6 million during the University’s fiscal year 1999, comprising more than 40 percent of the University’s $480.1 million in awards for use in 1999.

Juvenile Diabetes Foundation Awards $6.6 Million to U-M Medical School for Research on Complications of Diabetes

The Juvenile Diabetes Foundation International announced the opening at the U-M of a new $6.6 million Center for the Study of Complications in Diabetes. Each year, such complications rob millions of Americans of their sight, mobility or their life. Many more of the country’s 16 million people with diabetes suffer heart problems, vision deficits, nerve damage and kidney failure, yet researchers do not fully understand why.

More than 60 percent of people with diabetes suffer from some form of progressive nerve damage, or neuropathy, in one or more of their arms, legs or feet. It affects those diagnosed with Type 1 (juvenile) and Type 2 (adult onset) diabetes. Another of the most common diabetes complications is retinopathy, or progressive damage of the retina due to the deterioration of small blood vessels that supply the retina with oxygen and nutrients.

“I describe diabetic neuropathy to my patients as Alzheimer’s disease of the peripheral nerves,” says Douglas A. Greene, M.D., until recently director of the Center, professor of internal medicine, and director of the Division of Endocrinology and Metabolism. “It is a degeneration of the nerves, and it’s a dynamic process in which degeneration and regeneration are occurring simultaneously.”

Greene has devoted much of his career to understanding and treating diabetes complications. He coordinated much of the diabetes work at the U-M as director of the Michigan Diabetes Research and Training Center before leaving, in the spring, to become executive vice president of clinical sciences and product development for Merck Pharmaceuticals.

The Juvenile Diabetes Foundation Center for the Study of Complications in Diabetes at the University of Michigan will sponsor several related research projects on the role of blood sugar, or glucose, in the development of diabetes complications. Among the lead researchers is Eva L. Feldman, M.D., Ph.D., who will also serve as the associate director of the Juvenile Diabetes Foundation Center in addition to her appointment as an associate professor of neurology in the U-M Health System.
Depression Can Be Bad for Your Physical Health, New Study of Americans Over 70 Shows

Depression, in older people, can be as dangerous to one’s health as smoking. Older Americans who have symptoms of depression are as likely as those who smoked to develop a new disease within two years, according to a U-M study involving more than 6,000 Americans 70 years of age or older.

The study, presented at the annual meeting of the Gerontological Society of America in November, 1999, was conducted by Caroline S. Blaum, assistant professor of internal medicine. It is based on data from the U-M Health and Retirement Study, funded by the National Institute on Aging.

“The relationship of depression, disease and disability is complex,” says Blaum, who is also an assistant research scientist at the U-M Institute of Gerontology. “Not only do disease and disability lead to depressive symptoms, but depressive symptoms seem to be a precursor of the development of future disease. This effect is seen with relatively mild depressive symptoms such as decreased energy and restless sleeping, not just severe clinical depression.”

To evaluate the link between disease and depressive symptoms, Blaum analyzed data collected from the same group of older people in 1993 and again in 1995. The population-based study contains extensive information on physical, mental, financial, and emotional health, as well as a wide range of demographic and behavioral information for a nationally representative sample of Americans born in 1923 or before.

At the start of the study, the average age of respondents was 77 years. Approximately 62 percent were female, and 87 percent were white. Respondents had an average of 2.1 chronic diseases each. Between 1993 and 1995, Blaum found, 48 percent reported that they had developed new diseases, while 52 percent had the same self-reported “disease burden” with which they started the study.

Controlling for gender, marital status, education, the number of diseases at the start of the study, and the presence of mental or sensory impairments and disabilities, Blaum analyzed how age, race, body mass index, smoking, physical limitations and depressive symptoms were related to the odds of developing a new disease during the two-year period. The types of diseases included the most common chronic conditions of older adults, such as diabetes, stroke, arthritis, and cardiac disease.

Physical limitations, such as limitations in the ability to walk several blocks, climb stairs, or lift a 10-pound object, were the strongest predictors that a person would develop a new disease two years later, increasing the odds of developing at least one new disease by nearly 50 percent. But older people who smoked or had multiple symptoms of depression such as feeling lonely or sad in the past week were 34 percent more likely than those who did not to develop new disease, according to Blaum’s analysis.

“Other recent studies have suggested that depression and its symptoms are risk factors for cognitive decline and cancer,” says Blaum. “This study suggests that depressive symptoms may represent pre-clinical indicators of a wide range of future diagnosed diseases. Along with obesity and smoking, symptoms of depression may be a potentially modifiable risk factor for increased disease burden in older people. Clinical trials are needed to find out whether treatment of mild depression leads to decreased disease burden and improved function in older adults.”

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A new line of transgenic mice, created by researchers at the University of Michigan and the Hospital for Sick Children at the University of Toronto, will help scientists understand genetic and biochemical changes that cause a common form of human skin cancer called basal cell carcinoma.

“More than one million skin cancers are diagnosed in the U.S. each year and the majority are basal cell carcinomas,” says Andrzej A. Dlugosz, M.D., associate professor of dermatology and scientific director of the Cutaneous Oncology Program at the U-M Comprehensive Cancer Center.

Previous studies revealed that a mutation in a gene called “patched” (PTCH) was associated with development of human basal cell carcinomas, but it is not known how this genetic change causes a normal skin cell to become a tumor cell.

An initial study describing the new mouse model, published in the March 1, 2000, issue of *Nature Genetics* by Dlugosz and his co-investigators, strongly suggests that the protein Gli2 plays a key role in this process.

PTCH is an important component of a biochemical pathway, called the hedgehog pathway, which regulates embryonic development in organisms ranging from flies to humans. The hedgehog pathway is normally regulated in a very precise manner and is active only at certain times during development of different organs. Dlugosz explains that “when the PTCH gene is mutated, as in basal cell carcinomas, the hedgehog pathway is activated permanently.”

In earlier studies, Dlugosz and coworkers studied the hedgehog pathway in normal skin as a foundation for understanding how basal cell carcinomas arise. They found that the hedgehog pathway controls hair follicle development through a protein called Gli2, suggesting that this molecule may also play an important role in basal cell carcinoma development when the hedgehog pathway is deregulated. To test this hypothesis, the research team created mice which produce abnormally large amounts of Gli2 in their skin. By three months of age, these animals spontaneously developed multiple skin tumors that appeared strikingly similar to human basal cell carcinomas. Mouse tumors also expressed the same protein and RNA markers found in human tumors.

“These mice will help us learn more about the biology of these common skin tumors,” Dlugosz says. Basal cell carcinomas rarely metastasize and can be treated effectively with surgery, but the tumors can be disfiguring since they frequently occur on the face. New forms of non-invasive therapy would be beneficial, especially for high-risk patients who develop multiple tumors.

While other mouse models for basal cell carcinoma exist, Dlugosz says the U-M/Toronto model has advantages for use in scientific research. Other mice either cannot reproduce or the offspring die at birth. U-M/Toronto mice are viable and produce offspring. Plus, they produce tumors spontaneously without radiation exposure, which is commonly used to generate skin tumors in other mouse models.

First author of the *Nature Genetics* paper is Marina Grachtchouk, Ph.D., a research fellow in the U-M Medical School. Co-authors from the Hospital for Sick Children at the University of Toronto are Rong Mo, Sandy Yu, Xiaoyun Zhang and Chi-Chung Hui. Hiroshi Sasaki of Osaka University also is a co-author.

The investigators have applied for a joint patent on the new mouse model. The study was funded by the U-M Comprehensive Cancer Center, the U-M Center for Organogenesis and the National Cancer Institute of Canada.

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By depriving cancer tumors of the copper supply they need to form new blood vessels, researchers in the U-M Medical School have stopped the growth of the disease in a small group of patients with advanced cancer. Five of six patients whose copper levels were kept at one-fifth of normal for more than 90 days had no growth of existing tumors or formation of new ones, according to a paper published in the January, 2000, issue of Clinical Cancer Research. The sixth patient had progression of only one tumor; all other tumors within her body remained stable. Twelve other patients did not achieve the target copper level, or could not stay at the target level for 90 days, because of disease progression.

The finding is the first evidence in humans that physicians might fight multiple types of cancer by targeting copper as a ‘common denominator’ of angiogenesis — the process by which tumors grow the blood vessels that allow them to expand beyond a tiny cluster of cells. The copper strategy is not limited to a single type of cancer, as are other anti-angiogenesis agents now being studied.

Patients in the phase I trial at the U-M had metastatic cancer of the breast, kidney, colon, lung, skin, pancreas, prostate, throat, cartilage, blood vessels or endothelium. All had exhausted other conventional treatment options.

The U-M trial used oral doses of an inexpensive compound called tetrathiomolybdate, or TM, to lower patients’ copper levels. TM was originally developed for clinical use by George J. Brewer, M.D., Morton and Henrietta Sillner Professor of Human Genetics, to treat people with Wilson’s disease, a rare genetic disorder associated with excess copper. His work has shown TM to be the world’s most potent anti-copper agent, and safe to use.

Aware of earlier research indicating that copper is important for angiogenesis, Brewer did work in the early 1990s on animal cancer models treated with TM, with encouraging results. Then he teamed up with Sofia Merajver, M.D., Ph.D., associate professor of internal medicine, molecular genetics researcher, and oncologist in the Comprehensive Cancer Center.

Independently, Merajver was interested in exploring the inhibition of angiogenesis at very early stages in cancer development. Together with Brewer, she designed specific animal studies that allowed the team to test whether TM had the ability to prevent tumors from arising in animals at high risk for cancer. Her laboratory has also begun to uncover the molecular and cellular events involved in the inhibition of blood vessel growth by copper deficiency.

Their first results with humans actually came from a trial that was designed only to see how well TM could reduce copper levels in cancer patients, not to test its effect on the cancer itself. At all three daily dose levels given in the trial, copper levels were reduced to 20 percent of normal in four to six weeks. Neither the drug, nor the long-term copper deficiency, produced side effects.

“What began as a scientific hunch now appears to have potential as a simple but effective general anti-angiogenesis strategy,” says Brewer. “We are proceeding with a clinical trial aimed at accelerating TM-induced copper reduction and assessing its effect on advanced-stage cancer. Later this year, we hope to test this approach in 100 patients with five types of less advanced cancer.” Neither trial is currently accepting patients.

Adds Merajver, “These initial results suggest that the tactic of preventing angiogenesis through copper deficiency holds significant promise. Through this and other therapies, we may one day be able to turn cancer into a chronic or controllable disease or to contribute to its eradication. Still, much more research is needed before we can know the full potential of anti-angiogenesis.”

Angiogenesis happens in the body all the time, whether to repair a wound or help with the normal growth of children’s bodies. It occurs through a so-called angiogenesis “cascade” — a series of biochemical steps by which cells make and secrete molecules that initiate the growth of capillaries. After the job is done, other molecular “factors” turn off the angiogenesis process. But...
cancer cells use this normal process for a nefarious purpose — creating an imbalance of angiogenesis activators that overrides the inhibitors and gives the nearby tumor ready access to a blood supply. This creates a vicious cycle of growth that allows tumors to grow faster than the body can respond.

In recent years, researchers have found that copper is a common denominator to several of the key factors that activate the angiogenesis process. Specifically, it acts as a co-factor, or helper, to molecules known as basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and angiogenin. Without copper, the molecules can’t function and construction of blood vessels stops.

That’s why TM makes such a good choice, Brewer explains. It binds with copper and protein, making a stable compound that can’t be used by tumor cells or any other part of the body. Taken at mealtime, TM prevents the body from processing and absorbing the copper in food as well as the copper normally found in saliva and gastric secretions. Taken between meals, TM is absorbed into the blood and binds copper to blood protein. In either case, the TM-protein-copper complex does not interact with other biological molecules and is excreted.

The discovery of TM’s potential effect on cancer grew directly out of Brewer’s decades-long research on trace metals’ importance to the body. He began by examining the role of zinc in sickle-cell anemia, a disorder of the red blood cells, and unexpectedly found that zinc acetate reduced the level of copper in the blood of some patients. This gave him the idea to test the compound’s effect on the dangerously high copper levels in the systems of patients with Wilson’s disease, a potentially fatal recessive genetic condition that strikes 5,000 teen-agers and young adults each year. Finding that zinc acetate brought the patients’ serum copper levels under control regular, without side effects, he sought and received FDA approval for the compound.

But he needed a faster-acting compound to bring copper levels under control quickly. That compound turned out to be TM, now in clinical trials at the U-M General Clinical Research Center. To date, 63 Wilson’s disease patients have come to the U-M for eight weeks of treatment with TM to lower their copper levels, then returned home to take zinc acetate and follow a copper-restricted diet to maintain their copper levels.

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M-CARE: It’s Award-Winning

M-CARE, the University of Michigan Health System’s managed care organization, one of a few in the nation owned by an academic institution, recently has received several awards for its excellence in the delivery of health care. M-CARE’s high praise came from:

- The National Committee for Quality Assurance
- HealthGrades.com
- Greater Detroit Area Health Council’s 1999-2000 Consumer Guide to HMOs

M-CARE received a “commendable” accreditation rating from the Committee, an independent organization which evaluates how a health plan manages all parts of its delivery system in order to continuously improve health care for its members. M-CARE was one of five commercial, Medicare or Medicaid HMOs in Michigan to receive a “commendable” rating. “The accreditation demonstrates in a measurable way M-CARE’s commitment to clinical and service quality,” says Robert Church, D.O., M-CARE’s medical director. “Coupled with our very positive HEDIS scores, the accreditation shows that M-CARE is providing the health care people need with the quality and service they expect.” (HEDIS, which stands for Health Employer Data and Information Set, is the nation’s premier measurement tool for managed care.)

The National Committee for Quality Assurance also selected M-CARE for inclusion in a new book the Committee produced with support from Pfizer, Inc. Entitled Quality Profiles: In Pursuit of Excellence in Managed Care, the publication is a compendium of case studies to showcase outstanding quality improvement efforts. M-CARE was one of 38 health plans chosen from NCQA-accredited plans nationwide and the only plan in Michigan to be highlighted. “M-CARE’s inclusion in Quality Profiles is a true mark of distinction,” says Zelda Geyer-Sylvia, executive director of M-CARE. “Everyone in the M-CARE organization is committed to providing the highest quality care that we can, and being chosen for Quality Profiles is recognition of our ongoing efforts.”

- HealthGrades.com
  M-CARE received 76 points out of 100, the highest score in Michigan, from HealthGrades.com, an Internet-based firm providing information to consumers to help them select providers of health care. The firm used HEDIS data to grade nearly 250 HMOs from 39 major metropolitan areas in the U.S. M-CARE met or exceeded the national average in all categories evaluated by HealthGrades.com.

- Greater Detroit Area Health Council’s 1999-2000 Consumer Guide to HMOs
  The Council, a non-profit coalition of more than 100 organizations, used a five-star rating system to rate 16 HMOs in a number of categories. M-CARE was the only plan in Michigan to receive any five-star ratings, which they received in the “Staying Healthy” category.

M-CARE has more than 180,000 members and contracts with more than 2,000 employer groups. With field offices in Flint and Southfield, M-CARE has more than 5,000 physicians and over 40 hospitals in its 19-county commercial provider network, and over 3,000 physicians and 42 hospitals and health centers in its six-county Medicare network. M-CARE offers HMO and Point of Service as well as Medicaid and Medicare plans.

For more information about M-CARE, visit their Web site at www.mcare.org.
Anatomy and Cell Biology Becomes Cell and Developmental Biology

When the U-M Medical School opened its doors in 1850, a professorship in anatomy was one of the six established professorships comprising the medical faculty. For the next hundred years, the Department of Anatomy at Michigan developed along the traditional lines of teaching and research in gross anatomy, microscopic anatomy, embryology and neuroanatomy. In the process, the department produced some major scholars in the field, including James McMurrrich (gross anatomy), George Streeter (embryology), Carl Huber (neuroanatomy), Bradley Patten (embryology), and Elizabeth Crosby (neuroanatomy).

The Department retained its traditional orientation and areas of teaching and research emphasis until the 1970s, when sweeping changes in the biomedical research arena began to pull apart the monolithic bases of traditional preclinical disciplines. One reason for this change was the proliferation of many research-oriented professional societies, such as those of cell biology and the neurosciences, and the increasingly interdisciplinary nature of research in the field. The change in name to the Department of Anatomy and Cell Biology more than 10 years ago was a reflection of those trends.

Although the related disciplines of cell and developmental biology have historical scientific roots in the discipline of anatomy, both have incorporated and come to rely upon techniques of modern molecular biology. This has required a substantial movement away from classical anatomical methods of research. Thus at the end of 1999, the Department of Anatomy and Cell Biology became the Department of Cell and Developmental Biology, its evolution in many respects mirroring the historical changes in the discipline of anatomy throughout the century.

Bruce Carlson, Ph.D., chairs the Department of Cell and Developmental Biology. While Carlson is on sabbatical this year, Michael Welsh, Ph.D., professor of cell and developmental biology, is acting chair. Even as the academic discipline of anatomy has evolved into the interrelated disciplines of cell and developmental biology, the teaching of anatomy remains an integral and essential element of the Medical School curriculum.

To learn more about the Department of Cell and Developmental Biology, visit the department Web site at: www.med.umich.edu/cdb/index.html.

New Peptide Blocks

Medical School scientists have developed a new cancer-inhibiting peptide, a chain of amino acids, that has proven to be effective at preventing metastatic prostate cancer in laboratory rats from spreading to other organs.

Rats treated systemically with the new peptide developed smaller primary tumors and fewer lung metastases than untreated rats and showed no toxic side effects from the treatment. The peptide was effective even if primary tumors were allowed to grow to a large size before surgery and beginning peptide treatment. If future studies show the peptide works as well in humans, it could be the basis for a new approach to cancer therapy.

In an article published in the January 15, 2000, issue of Cancer Research, U-M scientists presented results from an extensive series of experiments which document the peptide’s ability to block cancer cells’ invasive activity and limit the growth and spread of tumors in laboratory rats. Donna L. Livant, Ph.D., assistant professor of cell and developmental biology, created the peptide by changing just one amino acid in a short sequence of a common blood protein called fibronectin, which circulates freely through the body in blood plasma, lymph, serum and interstitial fluid around cells.

When tissue is damaged, fibronectin at the injury site fragments and diffuses outward. Unlike intact fibronectin, which is present everywhere in the body, these fragments bind to fibronectin receptors on cells surrounding damaged tissue, which stimulates them to invade and repair the injury. The downside to this process, according to Livant, is that cancer cells can mutate so that intact fibronectin stimulates them to invade surrounding tissue also. “Cancer is the price we pay for our ability to heal from wounds,” Livant says.

“When intact fibronectin stimulates cancer cells to invade, they can easily reach the blood or lymphatic system and metastasize or spread to other parts of the body.”

In early cell culture studies, Livant discovered that metastatic tumor cells are not invasive unless serum — the fluid component of blood that remains after clotting — is present. “No one realized serum was required, because no one had studied cancer cell invasion in the absence of serum before,” Livant explains. Additional studies showed that plasma fibronectin was the only part of serum required for invasion. Finally, Livant isolated one specific peptide in fibronectin called PHSRN that triggered the invasion process.

Key Component of Bio-Artificial Kidney Moves Concept Closer to Reality: Clinical Trials May Begin Soon

Researchers at the University of Michigan are developing a bio-artificial kidney that uses living kidney cells to duplicate nearly all the functions of a healthy organ. While still in the experimental stage, the bio-artificial kidney could one day provide life-saving treatment for thousands of people with serious kidney disease.

“The kidney is the first human organ for which a mechanical substitute — the kidney dialysis machine — was designed,” says H. David Humes, M.D., professor of internal medicine. “We believe it also will be the first organ to have a fully functioning, implantable substitute created with the new science of tissue engineering.”

Humes and his U-M research team recently completed animal testing of a key component of the bio-artificial kidney, called a Renal Tubule Assist Device. This device is designed for use outside the body to treat acute kidney failure. Each year in the United States, about 190,000 people face this life-threatening condition, in which the kidneys suddenly shut down as a result of infection or injury. Individuals with acute renal failure typically spend at least 10
Spread of Prostate Cancer in Rats

“This PHSRN sequence on fibronectin fragments binds to the fibronectin receptor on many types of epithelial cells and stimulates them to migrate into damaged tissue,” Livant explains. “Metastatic prostate cancer cells also express the fibronectin receptor, but unlike normal cells, invasion is stimulated when their fibronectin receptor encounters the PHSRN sequence of intact fibronectin. This interaction triggers a process that stimulates malignant cells to invade surrounding tissue, as well as blood and lymphatic vessels. Once tumor cells have entered blood and lymphatic vessels, the process also stimulates them to leave the vessels to colonize distant sites.”

Using knowledge of the biochemistry of the fibronectin receptor site, Livant substituted the amino acid cysteine for arginine in the PHSRN sequence. “We speculated that cysteine might interact with the PHSRN-binding pocket of the fibronectin receptor in such a way as to block binding and prevent triggering cancer cell invasion,” she says.

Livant tested this new peptide derivative, which she calls PHSCN, on human and rat prostate cancer cell lines in culture and found it to be a powerful cell invasion inhibitor. She then tested it on laboratory rats injected with 100,000 cells from a naturally occurring, metastatic rat prostate cancer cell line called MAT-LyLu, which can kill a rat in just 25 days. Experimental rats in the study received intravenous injections of the new peptide three times each week; control rats received no treatment.

After 16 days of tumor growth and five PHSCN injections, the mean diameter of tumors in treated rats was less than 0.5 millimeters. The mean diameter of tumors in untreated rats was 1.8 centimeters, a 2,000-times larger volume. Untreated tumors had more than 10 times the blood vessel density found in tumors from treated rats. This is significant, because tumors must have a blood supply to grow.

To more accurately model clinical situations, Livant did not begin intravenous therapy in another group of rats until after surgically removing their large, primary tumors. Rats in this group which first received PHSCN 24 hours after surgery developed 99 percent fewer visible lung metastases and 95 percent fewer microscopic lung micrometastases than rats treated with surgery alone.

The exact mechanism of PHSCN’s anti-cancer activity remains unknown, although Livant has several possible explanations to test in future research. Her goal is to discover why this new peptide is so effective at preventing malignant cells from spreading and how it blocks the growth of blood vessels into the primary tumor.

“Most scientists think cell adhesion is the most important factor in metastasis,” Livant says. “But we believe aberrantly regulated or uncontrolled cell migration will prove to be equally important. There appears to be a biochemical ‘on switch’ controlling tumor cell movement, which may be activated by the defective receptor pattern of key receptors on cancer cells. Our goal is to learn how to use this new peptide to turn that switch off.”

Co-authors from the Medical School include R. Kaye Brabec, research associate; Kenneth J. Pienta, M.D., professor of internal medicine and professor of surgery; David L. Allen, Ph.D., post-doctoral research associate; Kotoku Kurachi, Ph.D., professor of human genetics; Sonja Markwart, research associate; and Ameet Upadhyaya, research associate. The U-M holds several patents on the PHSCN peptide related to the diagnosis and treatment of cancer. The study was funded by the March of Dimes, the National Institutes of Health and the U-M Office of the Vice President for Research.

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The purple sea urchin, Strongylocentrotus purpuratus, is a common marine invertebrate of the Pacific coast. Its transparent embryos grow rapidly in sea water cultures, making the sea urchin an ideal subject for research in cell migration and in embryonic development.

days in intensive care attached to a hemofiltration unit, which removes toxic waste products from their blood. Even with advanced medical care, more than 50 percent of these patients die before their kidneys can recover.

In a study published in the May, 1999, issue of Nature - Biotechnology, Humes described how the Renal Tubule Assist Device, connected to a standard hemofiltration unit, helped improve kidney function in laboratory animals with acute renal failure.

According to Humes, kidney cells lining hollow fibers in the device reabsorb vital electrolytes, water and glucose filtered out of blood during hemofiltration, in addition to producing other important molecules. Without these substances, the patient cannot fight off infections and maintain a normal fluid balance. In Humes’ study, the device reabsorbed about 50 percent of water and other important molecules, an amount similar to the reabsorption capacity of a normal kidney.

Pending FDA approval, human clinical trials for the Renal Tubule Assist Device in patients with acute kidney failure could begin as early as this fall. Within five years, Humes hopes to develop additional components of the bio-artificial kidney for patients with chronic renal failure — a gradual deterioration of kidney function that currently affects over 300,000 people in the United States, a number growing by about six percent each year.

“Our goal is to bring all the components for a bio-artificial kidney together in one implantable device that will carry out all the functions of a natural kidney,” Humes says. “We hope that one day it will be available as a universal-donor organ. This could eliminate the shortage of kidneys for transplant, end long waiting times for transplant organs, and replace dialysis as a treatment for chronic renal failure.”

Research on the bio-artificial kidney is being conducted at the Department of Veterans Affairs Ann Arbor Healthcare System. Funding to support the research is provided by the National Institutes of Health, the VA Research Service and Nephros.
New Surgical Technique Will Give Baby Jacob Prosthetic Eyes

Toddler Jacob Johnson of Grand Rapids, born with a rare condition called anophthalmia, has no eyes. He suffers from a total absence of ocular soft tissue and has no optic nerves. His eye sockets are also smaller than in a normal infant.

While Jacob’s blindness cannot be overcome, it will be possible to provide him with a normal appearance thanks to a new surgical technique developed by Christine C. Nelson, an ophthalmic plastic surgeon and associate professor in the Department of Ophthalmology and Visual Sciences in the U-M Medical School. Nelson’s surgery will make it possible for Jacob to eventually be fitted with prosthetic eyes. Jacob was referred to Nelson by his Grand Rapids ophthalmologist, Patrick Droste, M.D.

In order to prepare his eye sockets for the eventual prostheses, Nelson transplanted amniotic membrane within the bony structure of Jacob’s two orbits. She then placed two conformers, synthetic “shells,” inside the orbit that will help his sockets to open and expand.

Parents of children who are born with bilateral anophthalmia must deal with the realization that their children will be blind and disfigured. “Dealing with anophthalmia is like a roller coaster,” says Jacob’s mother, Michelle. “Sometimes it just hits you like a ton of bricks. But as time passes and we see how happy Jacob is, the pain lessens.” While blindness cannot be helped, disfigurement can be essentially eliminated by the use of carefully created prosthetic eyes that are produced by an ocularist, a person who combines artistry and engineering. The ocularist works closely with the ophthalmologist and the patient to create life-like artificial eyes that fit and move comfortably within the sockets. They are made of polymethylmethacrylate, the same material that is used to make hard contact lenses.

In order to prepare for a cosmetically pleasing prosthesis, it is critical to stimulate the socket early so that it can become large enough to accommodate a series of artificial eyes as the baby grows through childhood. The psychological benefits of having prosthetic eyes that are reasonably sized for a child’s growing face and that are painstakingly painted to mimic an organic eye are enormous.

The challenge is to find a way to stimulate the bone so that it grows and retains its shape as it expands. In microphthalmia, where the sockets are small but there is some remnant of soft tissue or a cyst that stimulates the socket, conformers alone often suffice. In anophthalmia, however, nothing has caused the socket to expand. In fact, the orbital bones grow much thicker, causing an even greater impediment to attempts to enlarge the sockets. In such cases, there is a limited amount of conjunctival tissue in the socket. The conventional treatment is to make an incision in the conjunctiva to allow for an expanded socket. The resulting gap, however, has to be bridged with biologically compatible tissue so that the net amount of conjunctiva can be increased.

Until recently, this bridge was mucosal tissue taken from the inside of the patient’s lip or cheek. While effective, this procedure created two wounds on the patient that required healing: the socket and the mouth. Further complicating an already difficult situation is the fact that infants do not have much mucosal tissue to harvest, making it sometimes necessary to do the surgery in stages.

Within the past year, a different procedure has been developed that avoids having to take tissue from a patient’s mouth — amniotic membrane transplantation. It was first introduced into the medical literature in the 1940s, but because it was difficult to store and transplant the tissue, it was not very successful until recently.

Amniotic membranes are donated by women who have undergone deliveries by Cesarean section. There are many advantages to using amniotic tissue rather than autologous tissue. Amniotic membrane forms the innermost layer of the fetal membrane. Because fetal membrane has antimicrobial properties, these transplanted membranes have fewer risks of developing postoperative infections. In addition, because there are no “live” cells, there is no risk of rejection or the graft-versus-host-disease that so commonly sabotages allograft transplants. There are also, large pieces of this tissue available for use. Finally, some physicians believe that amniotic membrane transplants have a cosmetic result that is superior to an autologous graft. “What’s even better,” says Nelson, “is that the wound seems not to hurt quite as much as when mucosal tissue was used. Any doctor who deals with kids knows that the number one priority is to minimize their pain if it’s at all possible.”

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Cochlear Implants:  
A Modern Hearing Miracle

For little Alivia Anderson, being able to hear the simple songs that toddlers love is a miracle of modern technology. Alivia, now almost two, was born with a malformation of the cochlea—the snail-shaped part of the inner ear that channels vibrations to the auditory nerve and the brain. Instead of a hollow spiral for sound to travel through, her cochleae are incomplete, preventing or limiting the ear-to-brain communication that makes hearing possible. But a cochlear implant, which Alivia received at 13 months of age as a patient in the U-M Cochlear Implant Program, has given her the gift of hearing. She is among the youngest ever to receive a cochlear implant.

The University of Michigan has been a leader in cochlear implants since the program, one of the nation’s first, was established 16 years ago. Since then, 200 adults and 300 children with hearing impairments have received cochlear implants at Michigan. Receiving a cochlear implant at Alivia’s age can be a distinct advantage, says Terry Zwolan, Ph.D., clinical associate professor and assistant research scientist in the department of otolaryngology and director of the U-M Cochlear Implant Program.

“We’re seeing that the sooner a child gets an implant, the sooner we can tap into speech and language development,” Zwolan says.

Cochlear implants transform speech and sound into electrical signals that the brain can interpret. They bypass the normal function of the outer ear, hair cells and cochlea, using surgically implanted electrodes and digital signal processors worn on the ear or body to do the work that the damaged or malformed ear structures can’t do.

The first step is capturing sound: A small magnetic microphone on the outside of the head, held in place by an implanted magnet, picks up sounds and sends them to a processor. After the processor’s programming translates the signals, the impulses travel through a coil to a receiver inside the ear. The implant transmits these signals through dozens of electrodes to the auditory nerve and brain, allowing the wearer to detect and understand speech and noise.

The model that baby Alivia was fitted with uses the first miniaturized device worn behind the ear, as well as a second processor the size of a pager worn on the body. It will allow her audiologists to fine-tune the sound she hears and the way speech is interpreted.

The technology of cochlear implants has improved greatly over the past decade. “In the early years, cochlear implants were suitable only for people who had some residual hearing,” says Zwolan. “Now we’re getting such nice results that criteria have expanded to include adults and children with severe to profound hearing loss.”

“Hearing aids and cochlear implants are very different instruments,” says Zwolan. “A hearing aid amplifies normal sound and uses the hearing that a person has to let them process that sound. It’s simply making sounds louder. A cochlear implant replaces the hearing inside the cochlea — that’s why it’s reserved for people who can’t benefit from hearing aids.”

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